REMARKS

Applicants acknowledge the Examiner's conclusion that the invention defined by the elected species, where the vitamin V is folate, the bivalent linker L comprises the tetrapeptide Asp-Arg-Asp-Asp-Cys, and the drug D is desacetylvinblastine monohydrazide, is patentable over the prior art. In addition, Applicants acknowledge that the Examiner has therefore expanded the search beyond the elected species in two respects, (i) where L is "any bivalent linker" and (ii) where D is "any drug."

Applicants also note the Examiner's acknowledgment that when the product claims are found allowable, the withdrawn process claims that depend from or otherwise include all of the limitations of the product claims will be rejoined.

Claims 11 and 49 have been amended. Applicants note with appreciation the Examiner's discovery of the punctuation error found in claim 11, which has been corrected herein. Claim 49 has also been amended to correct typographical errors. Claims 52-56 have been canceled without prejudice, and new claims 66-67 have been added. Support for the new claims is found throughout the specification, and in particular is found on page 18 of the application as filed. No new matter has been added by way of the amendments made or new claims added herein.

In the Office Action mailed June 29, 2007, the Examiner has rejected Applicants' claims 1-47, 49-55, 57-60, and 64-65 on several counts. Firstly, the Examiner has provisionally rejected 1-3, 47, 49-52, 55, and 57 on the grounds of nonstatutory double patenting over U.S. Application Serial No. 10/513,372 to Low et al. ("USA '372"). The Examiner contends that the rejected claims are obvious variants of the claims pending in USA '372. Secondly, the Examiner has rejected claims 1, 2, 4, 7, 10, 12-13, 17, 27-29, 31, 34, 38-40, 42, 44, 46, 49-52, 57-59, and 64-65 under 35 U.S.C. § 112, paragraph 2, as being indefinite. The Examiner contends that the rejected claims reciting the terms "analog or derivative thereof" and "derivative" are ambiguous. Thirdly, the Examiner has rejected Applicants' claims 1-2 and 52-55 under 35 U.S.C. § 102 as lacking novelty over Lu et al., in Cancer Immunology Immunotherapy, 51(3):153-62 (2002) ("Lu") contending that Lu discloses "a composition comprising a vitamin moiety (folate), a linker, and a drug (hapten)." Finally, the Examiner has rejected claims 1-47, 49-55, 57-60, and 64-65 under 35 U.S.C. § 103(a) as being obvious over Summerton et al. in U.S. Patent No. 6,030,941 ("Summerton") or Chari et al. in U.S. Patent No. 6,596,757 ("Chari").

Applicants have canceled claims 52-56 herein; thus, Applicants believe that the Examiner's rejection thereof is rendered moot, and request its withdrawal. Regarding the remaining claims, Applicants traverse each of the standing rejections and consider that the claims as amended herein are patentable for the reasons discussed below.

Nonstatutory Double Patenting Rejection

The Examiner has provisionally rejected Applicants' claims 1-3, 47, 49-51, and 57 on the ground of nonstatutory obviousness-type double patenting over USA '372. The Examiner contends that USA '372 and the instant application do not include patentably distinct claims because "both sets of claims are directed to conjugates comprising a vitamin, cleavable linker, and a drug, mitomycin." The Examiner suggests that the only difference is that the claims of USA '372 "are directed to the drug, mitomycin." Thus, the Examiner concludes that the person of ordinary skill in the art "would recognize" that the instant invention "encompasses" the invention of USA '372. Applicants disagree and traverse the rejection of those claims, believing that the rejected claims of the instant invention are not obvious variants of those currently pending in USA '372. Contrary to the Examiner's reading, the USA '372 claims are not encompassed by the instant claims.

Initially, Applicants point out to the Examiner that alleging that the instant claims "encompass" the claims of USA '372 is an improper basis and cannot support a rejection for nonstatutory double patenting. Applicants refer the Examiner to MPEP § 804, stating, "Domination and double patenting should not be confused" ("Domination by itself ... cannot support a double patenting rejection," citing *In re Kaplan,* 789 F.2d 1574, 1577-78, 229 USPQ 678, 681 (Fed. Cir. 1986); and *In re Sarrett*, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964)). Even so, Applicants believe that the Examiner has misread both the instant claims and those of USA '372, and therefore the Examiner's conclusion that the claims are obvious variants of each other is unsupported.

Applicants' claims 1-3, 47, 49-51, and 57 are drawn to vitamin receptor binding drug delivery conjugates that include a bivalent linker. As recited in independent claims 1, 49, 51, and 57, that linker must include "at least one releasable linker that is not a disulfide." To be clear, disulfide releasable linkers are certainly includable in the linker L as defined in Applicants' claim 1, but if present, at least one additional releasable linker must also be included in the bivalent linker L.

In contrast, the claims of USA '372 relied upon by the Examiner are drawn to cleavable linkers generally and do not include the specific requirement that at least one releasable linker is not a disulfide. Moreover, it is clear that in one aspect, the claims of USA '372 specifically include linkers that have only a single disulfide releasable linker, and no other releasable linker. Accordingly, Applicants respectfully point out that the instant claims cannot encompass those of USA '372, because Applicants' claims require that the bivalent linker include a releasable linker other than a disulfide, a limitation not found in the claims of USA '372. On the other hand, USA '372 includes linkers that fall outside the scope of the linker as defined in claims 1-3, 47, 49-51, and 57, namely linkers that include only a disulfide releasable linker.

Simply stated, a claim that excludes an element cannot be considered to be an obvious variant of another claim that includes that same element. Therefore, Applicants respectfully assert that the instant claims cannot be fairly characterized as being obvious variants of the claims of USA '372 when the former specifically exclude disulfide only releasable linkers and the latter specifically include the same.

Notwithstanding Applicants' argument to the contrary, should the Examiner yet consider that the instant claims are obvious variants of those in USA '372, Applicants respectfully request that the provisional rejection of claims 1-3, 47, 49-51, and 57 under nonstatutory double patenting over USA '372 be held in abeyance pursuant to MPEP § 804.

Indefiniteness Rejection under 35 U.S.C. § 112, ¶ 2

The Examiner has rejected claims 1, 2, 4, 7, 10, 12-13, 17, 27-29, 31, 34, 38-40, 42, 44, 46, 49-52, 57-59, and 64-65 under 35 U.S.C. § 112, paragraph 2, as being indefinite. The Examiner contends that the rejected claims reciting the terms "analog or derivative thereof" and "derivative" are ambiguous, stating that "one cannot ascertain which vitamin, vitamin receptor moiety, linkers, amino acids, mitomycin, and drugs that are encompassed by the instant invention."

Applicants traverse the Examiner's rejection under 35 U.S.C. § 112, paragraph 2. Applicants respectfully assert that the terms "analog or derivative thereof" and "derivative" are not ambiguous, and the person of ordinary skill in the art understands the meaning of the term analog as it applies to drugs, vitamins, vitamin receptor binding moieties, and mitomycins, and the meaning of the term derivative as it applies to drugs,

vitamins, vitamin receptor binding moieties, amino acids, and mitomycins in the instant claims.

MPEP § 2171 requires that claims be evaluated under Section 112, paragraph 2 to determine "whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." MPEP § 2173.02 titled "Clarity and Precision" also requires that an Examiner "should allow claims which define the patentable subject matter with a *reasonable* degree of particularity and distinctness." MPEP § 2173.02 further requires that "[i]n reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent" (citing *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000)). Thus, the MPEP and the case law that it cites requires that a claim define patentable subject matter with a reasonable degree of particularity and distinctness so that the claims apprise one of ordinary skill in the art of their scope and, therefore, what constitutes infringement of the patent.

For clarification, Applicants respectfully point out that, for example, claim 2 recites "vitamins, and vitamin receptor binding analogs and derivatives thereof" not simply analogs and derivatives of vitamins. In any event, the term *receptor-binding* analog or derivative as applied to a vitamin was well-known to those of ordinary skill in the art at the time the instant application was filed. In fact, for any compound that binds to a receptor, it was well-understood by persons of ordinary skill in the art long before the present application was filed what is meant by the phrase *receptor-binding*. It was understood by the skilled artisan well before the filing date of the present application that, if a compound exhibits specific binding in a receptor binding assay, such as Scatchard analysis, known as early as 1975 (*see, e.g.*, Carpenter, et al., *J. Biol. Chem.* vol. 250(11): 4297-4304 (1975)), the compound is a "receptor-binding" compound. Thus, a potential infringer would know exactly how to determine whether a compound is a receptor-binding compound, and, therefore, a potential infringer could easily understand whether or not he has made "a receptor-binding analog or derivative of the vitamin." If a potential infringer does a standard receptor binding assay using the analog or derivative of the vitamin, he can determine whether or not he has made "a receptor-binding analog or derivative of the vitamin."

The chemical structure of each of the vitamins described in the specification (*see, e.g.*, page 47, lines 18-21, lines 21-26; page 47, line 30 to page 48, line 13; page 48, lines 22-24) was well-known to those of ordinary skill in the art at the time the present application was filed. In fact, the chemical structures of the vitamins described in the specification have been well-known to persons of ordinary skill in the art for many years. It is also well-understood by the skilled artisan, and was well-understood at the time the present application was filed, that if the parent structure of a compound is changed, an analog or a derivative results. Thus, a potential infringer, knowing the chemical structure of each of the vitamins described in the specification, could easily understand whether or not he has made an analog or derivative of a vitamin. If a potential infringer changes the parent structure of a vitamin, he has made an analog or a derivative of the vitamin. Thus, the phrase "receptor-binding analog or derivative of the vitamin" is not indefinite.

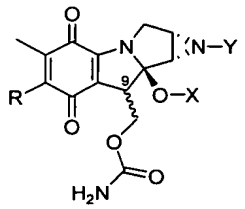
Moreover, examples of receptor-binding analogs and derivatives of vitamins have been described in the prior art evidencing that it is well-known what the phrase "a receptor-binding analog or a derivative" of a vitamin means. In support of the arguments made herein that the person of ordinary skill in the art understood what is meant by a "vitamin receptor binding analogs and derivatives" of vitamins, Applicants are filing a Supplemental Information Disclosure Statement to submit fifty-five journal articles and several issued U.S. patents. The Supplemental Information Disclosure Statement is transmitted herewith.

Those journal articles and U.S. patents also evidence that it is well-known to a skilled artisan what the phrase "analog or a derivative" of a vitamin means. In addition to that knowledge already possessed by the person of ordinary skill in the art, Applicants have also provided a number of further illustrative examples of vitamins, and analogs and derivatives thereof that bind to vitamin receptors (*see*, pages 47-48 of the specification as filed).

Similarly, the person of ordinary skill in the art is quite familiar with analogs and derivatives of drugs, such as the drug mitomycin highlighted by the Examiner. Like the vitamin receptor binding analogs and derivative, the chemical structure of each of the drugs illustratively described in the specification (*see, e.g.*, page 49, line 31 to page 50, line 19) was well-known to those of ordinary skill in the art at the time the present application was filed. In fact, the chemical structures of the drugs described in the specification have been well-known to persons of ordinary skill in the art for many years. It is also well-understood by the

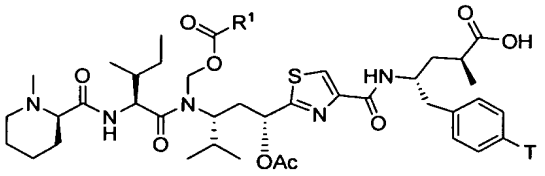
skilled artisan, and was well-understood at the time the present application was filed, that if the parent structure of a compound is changed, an analog or a derivative results.

For example, mitomycins, the drugs highlighted by the Examiner, include the following formulae:



Factor	R	X	Y	C-9
A	OCH_3	CH_3	H	α
B	OCH_3	H	CH_3	β
C	NH_2	CH_3	H	α
D	NH_2	H	CH_3	β
E	NH_2	CH_3	CH_3	β
F	OCH_3	CH_3	CH_3	α
J	OCH_3	CH_3	CH_3	β

In contrast, tubulysins include the following different formulae:



Factor	R^1	T
A	$(CH_3)_2CHCH_2$	OH
B	$CH_3(CH_2)_2$	OH
C	CH_3CH_2	OH
D	$(CH_3)_2CHCH_2$	H
E	$CH_3(CH_2)_2$	H
F	CH_2CH_3	H
G	$(CH_3)_2C=CH$	OH
H	CH_3	H
I	CH_3	OH

Upon viewing the foregoing, the person of ordinary skill in the art can determine on sight which compound is a mitomycin and which compound is a tubulysin. That skill should not be surprising, else the chemical nomenclature used to identify such drugs and distinguish them from other drugs would be useless. Further, it is clear from the above, that for example, the mitomycins and the tubulysins are not individual drugs, but instead each are families of drugs. In fact, the skilled person has already recognized how they should be grouped and

subsequently has named each unique compound with an additional letter, e.g., tubulysin A, tubulysin D, to distinguish members of the family. Hence, the skilled person already knows that for example tubulysin A is the tyrosine-like analog of tubulysin D, and will immediately recognize other analogs and derivatives of these and other drugs. In the same way, further modifications of drugs, such as the mitomycins and the tubulysins will be immediately recognized as analogs and derivative of those drugs. Thus, a potential infringer, knowing for example the chemical structure of a given drug like a mitomycin or a tybulysin, could easily understand whether or not he has made an analog or derivative of a drug. If a potential infringer changes the parent structure of a drug, he has made an analog or a derivative of the drug. Thus, Applicants believe that the term "drug, or an analog or derivative thereof" is not indefinite.

Finally, the person of ordinary skill in the art is quite familiar with derivatives of amino acids. Amino acids are simply compounds that include both an amino group and an acid group, as the name dictates. Amino acids are well-known to the person of ordinary skill in the art. Amino acids may be naturally occurring or not, and include those of non-natural stereochemistry, i.e. D-amino acids. Other amino acids may be metabolites of naturally occurring amino acids. Further, the amino acids also often include side chains. Regarding derivatives of amino acids, the person of ordinary skill in the art knows that the amino group, the acid group, and/or even the side chain groups may be modified to make derivatives of those amino acids. Even so, such derivatives are recognized by the person of ordinary skill in the art, and can on sight be called amino acid derivatives. Thus, a potential infringer, knowing for example the chemical structure of a given amino acid, could easily understand whether or not he has made a derivative of an amino acid. If a potential infringer further functionalizes the amino group, the acid group, and/or the side chain group(s), he has made a derivative of the amino acid. Thus, Applicants believe that the term "amino acid, or a derivative thereof" is not indefinite.

Consequently, Applicants contend that claims 1, 2, 4, 7, 10, 12-13, 17, 27-29, 31, 34, 38-40, 42, 44, 46, 49-52, 57-59, and 64-65 in the instant application are not indefinite under 35 U.S.C. § 112, paragraph 2 based on the terms "analog or a derivative" or "derivative" as used with reference to the vitamins, vitamin receptor moieties, linkers, amino acids, mitomycins, and drugs recited in those claims. The claims define patentable subject matter with more than a reasonable degree of particularity and distinctness. As a result, the claims clearly apprise one of ordinary skill in the art of their scope and, therefore, what

constitutes infringement of the patent. Applicants respectfully request the withdrawal of the rejection of claims 1, 2, 4, 7, 10, 12-13, 17, 27-29, 31, 34, 38-40, 42, 44, 46, 49-52, 57-59, and 64-65 under 35 U.S.C. § 112, ¶ 2.

Novelty Rejection under 35 U.S.C. § 102(a)

The Examiner has rejected claims 1-2 as lacking novelty over Lu. The Examiner contends that Lu describes a conjugate falling within the scope of Applicants' claims, stating that Lu discloses "a composition comprising a vitamin moiety (folate), a linker, and a drug (hapten)," and referring to Figures 1, 4, and 5 on pages 154 and 158. Applicants disagree and traverse the rejection, considering that claims 1-2 are novel over Lu simply because, contrary to the Examiner's reading, Lu's conjugate "comprising a vitamin moiety (folate), a linker, and a drug (hapten)" does not include the releasable linker required by Applicants' claims 1-2.

Anticipation exists only if all the elements of the claimed invention are present in a product or process disclosed, expressly or inherently, in a single prior art reference. *Hazeltine Corp. v. RCA Corp.*, 468 U.S. 1228 (1984).

Lu describes a single folate linked conjugate of FITC that may be used in the treatment of cancers by immunotherapy. Immunotherapy depends upon a complex process called antibody-dependent cellular cytotoxicity (ADCC). ADCC is a two step process that begins with the conversion of tumor cells "from a immunogenic state to a highly immunogenic state by the targeted enrichment of their cell surfaces with a novel hapten" (Lu, p. 154, col. 1). Once "decorated," the tumor cells are then recognized by the immune system "because of their extensive opsonization with anti-hapten antibodies" (*Id.*) and targeted for destruction by such cells, like F_c-expressing immune cells. Clearly, if the hapten is released during ADCC, the second step involving the immune-system mediated destruction of the tumor cell may not occur. Thus, a releasable linker in this arena of chemotherapy is incongruous. Hence, and consistent with this immunotherapy approach, the conjugate of Lu consists of folate covalently attached to FITC via the non-releasable linker ethylene diamine.

In contrast, Applicants' invention as defined by claims 1-2 is drawn to conjugates of a vitamin receptor binding moiety, a bivalent linker, and a drug, where the bivalent linker includes "at least one releasable linker." As stated above, the conjugate of Lu does not include a releasable linker. Thus, the conjugates described by Lu are unrelated to

those recited in Applicants' claims 1-2. Accordingly, Applicants request reconsideration of the rejection of claims 1-2 as lacking novelty over Lu, leading to its withdrawal.

Obviousness Rejection under 35 U.S.C. § 103(a) over Summerton

The Examiner has rejected Applicants' claims 1, 2, 47, 49-51, and 57 as being obvious over Summerton, stating:

> [I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Summerton et al [*sic*] and generate a conjugate comprising a vitamin moiety, linker, and drug because Summerton et al [*sic*] discloses that their polymer composition may comprise all of the components present in Applicant's [*sic*] vitamin conjugates.

In support of the rejection, the Examiner indicates that Summerton "discloses that one or more drugs may be attached to the polypeptide component of the [polymer] composition," that "[d]rug delivery is possible by linking or complexing the polymer-drug composition to a suitable ligand or receptor signal," and that "[i]t is generally desirable that the linkage between the polymer-drug composition and the ligand be cleavable."

Applicants do not believe that claims 1, 2, 47, 49-51, and 57 are rendered obvious by the disclosure of Summerton because Summerton fails to teach, describe, or suggest in any way Applicants' invention of a vitamin receptor binding drug delivery conjugate that includes a linker comprising a releasable linker in addition to or other than a disulfide. Summerton is directed toward drug delivery by a completely different mechanism. The Examiner points to the disclosure by Summerton of alternatives. However, on the one hand those alternatives are innumerable and not enabled, and on the other hand, some are incompatible with the conjugates disclosed therein. Finally, Summerton teaches away from vitamin targeting by admonishing endocytosis mechanisms in deference to mechanisms of direct entry into targeted cells.

Summerton is drawn to solving the problem of transporting drug conjugates across cell membranes. As a solution, Summerton discloses amphiphilic polypeptides containing multiple pairs of carboxylic acids for delivering drugs to cells. In particular, Summerton discloses that the polypeptides "exhibit solubility in both hydrophilic and lipophilic environments by undergoing a reversible pH-dependent transition from a low-pH, lipophilic form to a high-pH, hydrophilic form" (col. 1, ll. 13-16). Summerton states that the lipophilic form partitions from the low-pH environment of the extracellular environment into the lipid layer, and the hydrophilic form partitions preferentially from the lipid layer into the higher-pH aqueous compartment of the cell. That mechanism of drug delivery is important

because Summerton relies on the observation that "[m]ost solid tumor masses contain cells which are hypoxic (oxygen deficient), due to insufficient blood supply" (c. 20, ll. 45-46). Accordingly, Summerton states that "with the present method, hypoxic tumor cells, by virtue of their low pH environment, may be targeted by an antineoplastic drug linked to a polypeptide which is effective to partition into a membrane at the pH present in this extracellular environment" (col. 20, l. 64 to col. 21, l. 1).

In addition, Summerton characterizes direct entry into cells as preferred, and superior to other routes such as endocytosis. Summerton states that "direct cell entry is generally much faster than endocytosis ... transport occurs within a matter of minutes," whereas "endocytotic entry, on the other hand, generally takes many hours" (col. 21, ll. 11-16, emphasis added). Moreover, Summerton indicates that in addition to the more rapid entry using the direct entry of the polypeptide conjugates, direct entry provides better selectivity. As is well-understood by the person of ordinary skill in the art, selectivity in treating cancer cells compared to normal tissues is a critical feature of a successful therapy. Summerton further discourages endocytosis, emphasizing that in the process of endocytosis, "[i]n most cases, the endosome then merges with a lysosome, resulting in exposure of the internalized compound to degradative enzymes" (col. 2, ll. 25-27). Summerton recognizes that it would be "desirable to deliver compounds into the cell cytosol via a route which avoids exposure to lysosomal enzymes" (col. 2, ll. 33-35, emphasis added). Teaching away from endocytosis may stem from Summerton's misunderstanding of the nature of vitamin mediated delivery. For example, Summerton suggests that potocytosis is the operating mechanism, and assumes that there will be no merger with lysosomes. Summerton states that potocytosis "presents certain advantages" over endocytosis because the caveolae formed during potocytosis "do not merge with pre-lysosomes, and thus potential exposure of the composition to degradative enzymes is avoided" (col. 22, ll. 7-10). Thus, reading the teachings of Summerton as a whole, the person of ordinary skill in the art is discouraged from employing the mechanisms of endocytosis for delivering drugs to cells, and would not modify the teachings of Summerton to include vitamin targeting, which is known to include endocytosis mechanisms of cell entry.

In contrast, Applicants' invention as defined by claims 1, 2, 47, 49-51, and 57 is drawn to targeting cells for delivery of drug conjugates using vitamin receptor binding moieties. Unlike Summerton, which is focused on a different mechanism for transport, Applicants recognized that vitamin receptor targeting is an excellent method for delivering

drugs via conjugates of vitamins, and analogs and derivatives thereof. Applicants also appreciated that vitamin targeting could take advantage of two other properties, the selective targeting of certain cell types such as cancer cells due to the higher expression of, for example, folate receptors, and also the ability to transport drug conjugates into cells via the process of endocytosis. It is now well-established that many vitamins, such as folate, can enter cells via endocytosis. That endocytotic mechanism is also capable of delivering conjugates of those vitamins. Notwithstanding the teachings of Summerton, Applicants point out that they do not consider endocytosis to have any limitations as a drug delivery mechanism. Nevertheless, it is the teachings of Summerton that is before the skilled artisan, not the knowledge possessed by Applicants. Accordingly, Applicants contend that Summerton would not motivate the skilled artisan in the way the Examiner suggests to arrive at the invention defined by claims 1, 2, 47, 49-51, and 57. To do so, the person of ordinary skill in the art would have to forsake the direct entry into cells highlighted by Summerton and return to, as Summerton describes, the slower potentially enzyme-mediated degradative processes of endocytosis.

Finally, Summerton fails to suggest each and every element of Applicants' claimed invention. Applicants' invention as defined by claims 1, 2, 47, 49-51, and 57 requires that the linker include at least one releasable linker other than a disulfide. The only linker exemplified and described by Summerton as a cleavable linker is in fact a disulfide (*see*, Example 3). Thus, it cannot be fairly said that the claimed bivalent linker having "at least one releasable linker that is not a disulfide" is described or even enabled by Summerton in a way sufficient to satisfy the requirements of Section 112 of the Patent Law for the portions relied upon by the Examiner.

Applicants are not surprised that Summerton is so deficient in its description and enablement of either vitamin receptor ligands or of releasable linkers, because Summerton is describing a completely different principle for transporting compounds across cell membranes. That principle is the use of amphiphilic polypeptides as rapid direct entry mechanisms into cells. Summerton employs the polypeptide for its alpha helical forming properties, and its ability to fold differently between hydrophilic and lipophilic states, thus allowing it to traverse membranes to access the cytosol of the cell, by "wiggling" its way through. Thus, to modify Summerton to include a vitamin receptor binding ligand would render irrelevant the vast majority of what is emphasized by Summerton, namely the use of the polypeptide for both targeting and for entry in the cell. Such disclosure cannot be fairly

characterized as motivating the skilled person to make the modification of Summerton that the Examiner suggests.

Accordingly, Applicants contend that the person of ordinary skill in the art *would not* modify the polypeptides of Summerton with a vitamin receptor binding moiety, and *could not* include the necessary non-disulfide releasable linkers recited in Applicants' claims to arrive at the instant invention. Therefore, Applicants believe that the invention defined by claims 1, 2, 47, 49-51, and 57 is not rendered obvious by Summerton, and request reconsideration of the rejection under Section 103, leading to its withdrawal.

Rebuttal of Obviousness Rejection over Summerton based on Unexpected Results

Finally, even assuming arguendo that the Examiner has established a *prima facie* case of obviousness, and again Applicants contend that *prima facie* obviousness has not been established, the Examiner's Section 103 rejection of claims 1-47, 49-51, 57-60, and 64-65 is overcome based on the unexpected results obtained with Applicants' claimed methods and compounds for use in treating cancer.

The question of nonobviousness must turn on whether the *prima facie* case of obviousness of the claimed composition is rebutted by a showing of unexpected results. *In re Diamond*, 53 CCPA 1172, 360 F.2d 214, 149 USPQ 562 (1966). *In re Meinhardt*, 55 CCPA 1000, 392 F.2d 273, 157 USPQ 270 (1968). The Federal Circuit in *In re Dillon* concluded that a *prima facie* case of obviousness can be rebutted by "showing that the claimed compositions possess *unexpectedly improved properties or properties that the prior art does not have*" (919 F.2d 688, 692, 16 U.S.P.Q. 2d 1897, 1901 (Fed. Cir. 1990) (emphasis added)). Applicants' respectfully point out that as described in the Declaration of Dr. Christopher P. Leamon, filed under 37 C.F.R. § 1.132 and transmitted herewith, the vitamin receptor binding drug delivery conjugates defined by claims 1-47, 49-51, 57-60, and 64-65 exhibit unexpectedly high activity because the claimed compounds exhibit activity at doses far below the maximum tolerated dose, and moreover the claimed invention possesses properties not possessed by the prior art because the claimed compounds lead to complete responses in the treated animals.

As described in the Dr. Leamon's Declaration, four conjugate compounds representative of the instant invention were used in treating test animals with established tumors. Those four conjugates were prepared from four distinct chemical classes, vinblastines, epothilones, maytansines, and tubulysins. In each case, the claimed conjugate

compound outperformed the unconjugated compound, which had only a minor effect on tumor growth. Further, compared to the unconjugated compounds, the conjugates were highly potent at dosages far below their MTD. For example, as can be seen in Figures 2 and 4 of the Dr. Leamon's Declaration, the unconjugated compound was lethal before the end of the dosing period. Moreover, even at that maximum dose, the tumor continued to grow. In contrast, the claimed conjugates rapidly controlled tumor growth without the gross toxicity observed with the unconjugated compounds. This high level of activity is an unexpected result.

Stated another way, the claimed conjugates lead to an infinitely larger survival ratio (No. of surviving animals/No. of deaths) compared to the unconjugated compounds. As can be seen from Figures 2 and 4, all animals treated with the unconjugated compounds died by days 16 and 18, respectively (i.e. a survival ratio of 0 at day 18). In contrast, all animals that were treated with the claimed conjugates survived beyond days 43 and 47, respectively (i.e. an infinite survival ratio at day 43). An infinite difference in survival ratio is unexpectedly high.

Moreover, the claimed compounds also exhibit unexpected properties not possessed by the prior art. One unexpected property is a complete response to the conjugate by the tumor in up to 100% of the treated animals. As stated by Dr. Leamon, a complete tumor response is always unexpected in cancer therapy. Figures 1-4 show that each of the claimed conjugates was able to cause complete disappearance of the tumor in all 5 (100%) of the animals that were treated. A complete response was not observed in a single animal treated with any of the unconjugated compounds.

A second unexpected property of the claimed compounds not possessed by the prior art is a complete response without reoccurrence of disease. As described by Dr. Leamon, each of the claimed conjugates was administered over a period of between 5 and 19 days. Following the completion of the dosing period, monitoring of the animals was continued. In no case was significant tumor regrowth observed. That efficacy is contrasted to the behavior observed with the unconjugated vinblastine DAVLBH, namely the only unconjugated compound to show any tumor disappearance whatsoever. With unconjugated DAVLBH, tumor regrowth was rapid following the completion of the dosing period. Further, monitoring of the vinblastine and tubulysin conjugate-treated animals was continued for an extended period of time. As Figures 5 and 6 show, even after 72 and 100 days post treatment, respectively, no tumor regrowth was observed in any of the 5 treated animals

(100% non-recurrence). As stated by Dr. Leamon, a complete lack of tumor recurrence is also always unexpected in cancer therapy.

Finally as further evidence of the profoundly unexpected and improved properties of the claimed invention, the claimed conjugates are currently in Phase I and Phase II clinical trials in both ovarian and lung cancer treatments for submission to the FDA in Investigational New Drug Study Reports.

As discussed above, the Examiner relies on Summerton as a basis for rejecting Applicants' claims under Section 103. Summerton does not present any *in vivo* data whatsoever. Thus, Applicants respectfully assert that the results observed with the claimed invention are unexpected in three respects. The first is the unexpectedly high activity of the claimed compounds, i.e. infinite survival ratios compared to the zero survival ratio observed with the unconjugated compounds. The second is the unexpected property of complete tumor response in up to 100% of the test group. The third is the unexpected property of the complete absence of tumor regrowth in up to 100% of the test group.

Summerton does not provide any evidence that a complete response by a tumor to treatment could be obtained with any compound disclosed therein, nor in fact even makes any mention of it. Further, that reference relied upon by the Examiner does not provide any evidence that non-recurrence of tumors could be obtained upon treatment with any compound disclosed therein, nor in fact does it even make any mention of it. Thus, those same results obtained using Applicants' claimed conjugates are unexpected results.

Accordingly, even if the Examiner has made a *prima facie* case of obviousness, and Applicants contend that the Examiner has not, the Applicants have rebutted the Examiner's *prima facie* case by demonstrating that Applicants' claimed compounds have unexpectedly improved activities and properties that the prior art does not have. Hence, Applicants respectfully request that the rejection of claims 1, 2, 47, 49-51, and 57 as being obvious over Summerton be reconsidered leading to its withdrawal.

Obviousness Rejection under 35 U.S.C. § 103(a) over Chari

The Examiner has also rejected Applicants' claims 1-47, 49-51, 57-60, and 64-65 as being obvious over Chari, stating:

> "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a composition comprising a vitamin moiety, linker, and a drug because Chari et al [*sic*] disclose a composition that may contain the same components as that being claimed by Applicant [*sic*]. Thus, both Applicant and Chari et al [*sic*] disclose overlapping subject matter.

In support of the rejection, the Examiner indicates that Chari discloses "polyethylene glycol containing taxanes." In addition, the Examiner indicates that Chari discloses that such derivatives may be "linked to a cell binding agent" through, for example, a "thiol-containing group." The Examiner also indicates that Chari discloses that a "possible cell binding agent may be a vitamin."

Applicants note that Chari is useable as a reference under Section 103(a) only insofar as it qualifies as a reference as defined by 35 U.S.C. § 102(e), that based on its filing date of May 14, 2002. Accordingly, the Examiner is kindly directed to the declaration of Dr. Iontcho R. Vlahov, filed under 37 C.F.R. § 1.131, and transmitted herewith. That declaration with the accompanying Exhibit A establishes that the invention as defined by claims 1-47, 49-51, 57-60, and 64-65 was made prior to May 14, 2002, the filing date of Chari. Exhibit A of Vlahov's declaration includes photocopies of compound submission sheets that are filed in the ordinary course of business at Endocyte, Inc. when a new compound is prepared and characterized. Those compound submission sheets show the structures for several Examples included in the application as filed, each of which was prepared and characterized prior to the filing of Chari. Therefore, Applicants believe that Chari is not a valid reference under Section 103(a) and respectfully requests that it be removed from consideration, leading to the withdrawal of the rejection of claims 1-47, 49-51, 57-60, and 64-65 as being obvious.

CONCLUSION

The foregoing remarks are believed to fully respond to the Examiner's rejections. Applicants believe that the claims are in condition for allowance and respectfully request that all outstanding rejections are withdrawn and the application is passed to issuance.

Respectfully submitted,

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